Cooperative Study CSP #599

Transfusion Trigger after Operations for Patients with High Cardiac Risks (TOP)

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STATISTICAL ANALYSIS PLAN

Version Number 4

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Version 4

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LIST OF ABBREVIATIONS

Abbreviation	Definition
RBC	Red Blood Cells
Hb	Hemoglobin
ICU	Intensive Care Unit
IHD	Ischemic Heart Disease
PAD	Peripheral Arterial Disease
nHb	nadir Postoperative Hb
ACS	Acute Coronary Syndrome
OR	Odds Ratio
MI	Myocardial infarction
RCRI	Revised Cardiac Risk Index
CDW	Corporate Data Warehouse
CPT	Current Procedural Terminology
ICD-9	International Classification of Diseases
EKG (ECG)	Electrocardiogram
AKI	Acute Kidney Injury
ESRD	End Stage Renal Disease
RIFLE	Risk, Injury, Failure, Loss, ESRD, Criteria
CDC	Centers for Disease Control and Prevention
SIRS	Systemic Inflammatory Response Syndrome
WBC	White Blood Cells
CHF	Congestive Heart Failure
DAF	Death Ascertainment File
CRF	Case Report Form
CRP	Clinical Research Pharmacist
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CSPCRPCC	Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
CSSEC	Cooperative Studies Scientific Evaluation Committee
CK-MB	Creatine kinase MB
VAMC	VA Medical Centers
NODES	Network of Dedicated Enrollment Sites
DMC	Data Monitoring Committee
VA CIRB	VA Central Institution Review Board
IRB	Institution Review Board
HIPAA	Health Insurance Portability and Accountability Act
ITTRS	Interactive Touchtone Telephone Randomization System
FDA	Food and Drug Administration
RCRI	Revised Cardiac Risk Index
GCP	Good Clinical Practice
GCPMG	Good Clinical Practice Monitoring Group

GCPSRG	Good Clinical Practice Standards and Resource Group
BMI	Body Mass Index
HRC	Human Rights Committee
AE	Adverse Events
SAE	Serious Adverse Events
R&DC	Research & Development Committee
ICH	The International Conference on Harmonization
ICH-E2A	ICH Clinical Safety Data Management
SOP	Standard Operation Procedure
MedDRA	Medical Dictionary for Regulatory Affairs
CSRD	Clinical Science Research and Development
SAP	Statistical Analysis Plan
PHI	Personal Health Information
CFR	Code of Federal Regulations
FIPS	Federal Information Processing Standard
SSN	Social Security Number
SMART	Site Monitoring, Auditing and Resource Team
LSI	Local Site Investigator
ITT	Intent-to-Treat
CI	Confidence Interval
OR	Odds Ratio
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
RCT	Randomized Controlled Trial
R&D	Research & Development
SC	Study Coordinator
SI	Site Investigator
VA	Veterans Affairs

1. SUMMARY

The overall goal of the proposed study is to determine whether a liberal transfusion strategy (transfusion trigger at Hb<10gm/dl) in patients at high risk for postoperative cardiac events who undergo open vascular and general surgery operations is associated with decreased risk of adverse postoperative outcomes compared to a restrictive transfusion strategy (transfusion trigger at Hg < 7 gm/dl). This study will compare all-cause mortality and other complications between the liberal (transfusion trigger at Hb<10gm/dl) and restrictive (transfusion trigger at Hb<7gm/dl) transfusion policies for high cardiac risk patients who undergo surgical procedures. The study will randomize 1520 patients from 15 participating sites over a four-year recruitment period. The primary end point of the study is a composite event of 90-day all-cause mortality, myocardial infarction (MI), coronary revascularization, stroke, and acute renal failure after randomization. The study hypothesis is that the liberal transfusion policy group will have a lower composite event rate than the restrictive transfusion policy group. Secondary objectives of this study include: 1) to examine the effect of transfusion strategy on post-randomization infectious complications, 2) to examine the effect of transfusion strategy on post-randomization cardiac complications other than MI, 3) to examine the effect of transfusion strategy on all-cause mortality up to one year after randomization, 4) to examine the effect of transfusion strategy on a composite endpoint of all-cause post-randomization mortality, MI, coronary revascularization, acute renal failure, and stroke up to 30 days after randomization, and 5) to examine the effect of transfusion strategy on length of hospital stay.

This statistical analysis plan (SAP) is drafted after review of the current CSP-599 study protocol and case report forms (CRFs). Detailed information is given to aid in the production of the statistical output and the statistical section of the final study report, and potential manuscripts for publication. This document provides background of the study based on the protocol and describes the populations that will be analyzed. All subject characteristics and the efficacy and safety parameters that will be evaluated, along with the specific statistical methods, are described.

2. INTRODUCTION

2.1. Background

Blood is an indispensable product in modern medical practice.[1] Red blood cells (RBC) replace intravascular volume, improve oxygen delivery to tissues in situations of hemorrhage, and anemia[2] and consist one of the few treatments that adequately restore tissue oxygenation and maintain life when oxygen demand exceeds supply.[3,4] Currently there is no physiologic test to assist with clinical decision-making. The lack of sophisticated physiologically driven transfusion algorithms has led to the development of the "transfusion trigger" concept, which dictates that a specific level of hemoglobin (Hb) should be used to guide transfusion decisions. Historically, the widely accepted clinical standard has been to transfuse patients when the Hb level drops below 10gm/dl or the hematocrit falls below 30% and served as RBC transfusion guide for decades[4,5].

Blood is a finite resource whose collection depends on the availability of donors and its processing is costly and time consuming.[1,6,7,8,9,10-12] Therefore, clinicians sought to determine the safety of more restrictive blood transfusion strategies. Hebert et al.[13] studied the impact of transfusion strategy in the ICU setting. The authors demonstrated that a restrictive transfusion strategy that accepted Hb as low as 7gm/dl did not have an adverse impact on survival, although a post-hoc analysis[14] of this trial that included a subset of patients with known ischemic heart disease demonstrated a trend for increased mortality in the restrictive transfusion group.

Since then other randomized trials have examined the impact of transfusion strategy on specific patient populations using various combinations of restrictive and liberal thresholds, including trials in patients undergoing cardiac surgery[15], in patients undergoing hip replacement,[16] in patients with septic shock[17], and in patients with acute upper gastrointestinal bleeding[18]. These trials suggested a restrictive transfusion strategy was well tolerated in these specific populations and one trial[18] even demonstrated the restrictive transfusion strategy was superior.

Published guidelines[2,19-21] and health policy statements[22] place a lot of emphasis on the need for restrictive transfusion thresholds in a variety of clinical settings; at the same time, the guidelines acknowledge[21] that a substantial area of uncertainty remains and concerns the patients with underlying cardiovascular disease, a population that is more likely than any other

to be extremely sensitive to transfusion thresholds. Data on these high cardiac risk patients remain scarce, coming mainly from small trials and secondary analyses[23-24]. In the recently published TITRe2 trial[25] with 2007 patients undergoing cardiac surgery randomized to a liberal (trigger Hb < 9 gm/dl) or a restrictive (trigger Hb < 7.5 mg/dl) transfusion arm, the primary endpoint (a composite of a serious infection or an ischemic event at 90 days after randomization) was not different between the two groups. However, mortality at 90 days was more likely in the restrictive group.

As the world is progressively moving towards more restrictive transfusion standards, the unanswered question of transfusion thresholds in high cardiac risk patients has created a knowledge gap that requires urgent attention. Given the magnitude of ischemic heart disease (IHD) as health care problem[26], this uncertainty creates a critical patient safety issue.

In order to address this knowledge gap, we propose a randomized trial to compare two transfusion strategies in high cardiac risk patients undergoing vascular and general surgery operations. The study cohort will include patients with known history of IHD and IHD equivalent diseases (ischemic stroke, or peripheral artery disease [PAD]). PAD is a well-known marker of IHD and myocardial infarction represents the leading cause of mortality after PAD-related operations.[27] Furthermore, patients in the proposed study will not have their coronary artery lesions routinely repaired during or prior to the index operation, and therefore their risk of cardiac events postoperatively will remain at least as high as it was preoperatively.

2.2. Goal of the Study

The goal of the proposed study is to determine whether a liberal transfusion strategy (transfusion trigger at Hb < 10 gm/dl) in Veterans at high cardiac risk who undergo major open vascular and general surgery operations is associated with decreased risk of adverse postoperative outcomes compared to a restrictive transfusion strategy (transfusion trigger at Hb < 7 gm/dl).

3. STUDY OBJECTIVE AND ENDPOINTS

3.1. Study Objectives and Hypotheses

Primary Objective:

Objective 1: To examine the effect of transfusion strategies on a composite endpoint of all-cause post-randomization mortality, myocardial infarction (MI), coronary revascularization, acute renal failure, or post-randomization stroke in Veterans at high cardiac risk undergoing open surgical interventions.

Primary Hypothesis:

Hypothesis 1: A significantly smaller proportion of participants receiving blood under a liberal transfusion strategy will experience the composite compared to participants under restrictive transfusion strategy at 90 days after randomization.

Secondary Objectives:

Objective 1: To examine the effect of transfusion strategies on post-randomization infectious complications.

Hypothesis 1: A smaller proportion of participants receiving blood under a liberal transfusion strategy will experience post-randomization infectious complications compared to participants under restrictive transfusion strategy at 90 days after randomization.

Objective 2: To examine the effect of transfusion strategies on post-randomization cardiac complications other than MI.

Hypothesis 2: A smaller proportion of participants receiving blood under a liberal transfusion strategy will experience post-randomization cardiac complications other than MI compared to participants under restrictive transfusion strategy at 90 days after randomization.

Objective 3: To examine the effect of transfusion strategies on all-cause mortality during the one-year post-randomization follow-up.

Hypothesis 3: A smaller proportion of participants receiving blood under a liberal transfusion strategy will die from any cause compared to participants under restrictive transfusion strategy during one year follow-up after randomization.

Objective 4: To examine the effect of transfusion strategies on a composite endpoint of all-cause post-randomization mortality, MI, coronary revascularization, acute renal failure, or post-randomization stroke at 30 days after randomization.

Hypothesis 4: A smaller proportion of participants receiving blood under a liberal transfusion strategy will experience the composite endpoint compared to participants under restrictive transfusion strategy at 30 days after randomization.
Objective 5: To examine the effect of transfusion strategies on the length of hospital stay
Hypothesis 5: Liberal transfusion strategy will lead to a shorter length of hospital stay.

Tertiary Objective:
Objective: To examine the effect of transfusion strategies on the components of the primary endpoint.
Hypotheses: A smaller proportion of participants receiving blood under a liberal transfusion strategy will experience post-randomization death from any cause, MI, coronary revascularization, acute renal failure, or post-randomization stroke, compared to participants under restrictive transfusion strategy at 90 days after randomization.

3.2. Study Outcome Variables

3.2.1. Primary Outcome Variable

The primary outcome is defined as a composite endpoint of all-cause post-randomization mortality, myocardial infarction (MI), coronary revascularization, acute renal failure, or post-randomization ischemic stroke up to 90 days after randomization.

MI will be defined using the Third Universal Definition of Myocardial Infarction.[28]

Acute renal failure will be defined as Acute Kidney Injury stage III according to RIFLE criteria: Serum creatinine rise greater than 3 times that of baseline creatinine; or if baseline serum creatinine is greater than 4 mg/dl, then rise more than 0.5 mg/dl compared to baseline; or urine output less than 0.3ml/Kg/hr for 24 hours; or anuria for 12 hours. Baseline creatinine will be considered the creatinine upon admission prior to the index operation. The above urine output criteria will be only used for patients who are in the ICU and have precise monitoring of their urinary output. For patients on the surgical floor only serum creatinine changes will be used for assessment of this endpoint.

Coronary revascularization will be defined as a coronary artery bypass graft, or percutaneous coronary intervention (either angioplasty or stenting).

Stroke will be defined as new unilateral neurological deficit that lasts for more than 24 hours and is confirmed by a brain imaging modality (either computed tomography or magnetic resonance imaging study) demonstrating new brain infarct.

3.2.2. Secondary Outcome Variables

There are five secondary outcome measures based on their use in previous studies.
Outcome 1: A composite endpoint of post-randomization infectious complications at 90 days post-randomization: Infectious complications will include wound infections, pneumonia, and sepsis.

Wound infection will be defined according to the Centers for Disease Control and Prevention (CDC) guidelines as a) positive wound culture, or b) drainage of pus from a wound, or c) suspicion of wound infection that was drained operatively.

Pneumonia will be defined according to the CDC definition as chest radiograph or imaging with new or progressive infiltrate, consolidation, cavitation, or pleural effusion and any of the following: new onset of purulent sputum or change in character of sputum, or organism isolated from blood culture, trans-tracheal aspirate, bronchial brushings, or biopsy.

Sepsis will be defined as a combination of two of the following systemic inflammatory response syndrome (SIRS) criteria, plus suspected or present source of infection. SIRS criteria will include the following: temperature greater than 38C, heart rate greater than 90 beats/min, WBC > 12,000 or < 4,000, or > 10% bands.

Outcome 2: A composite endpoint of cardiac complications (other than MI) at 90 days post-randomization: Cardiac complications will include new cardiac arrhythmias that necessitate new treatment, congestive heart failure (CHF) exacerbation, and cardiac arrest.

The diagnosis of cardiac arrhythmias will be based on EKG findings. Only arrhythmias that result in initiation of new treatment regimen (to include medications, implantable devices, or surgical intervention) during hospitalization will be recorded.

CHF will require at least one of the following symptoms or signs new or worsening: dyspnea at rest, orthopnea, or paroxysmal nocturnal dyspnea and radiological evidence of heart failure or worsening heart failure and increase/initiation of established treatment.

Cardiac arrest will be defined as the cessation of cardiac pump function activity that results in loss of consciousness and absence of circulating blood flow as evidenced by absent

carotid pulse. Only episodes of cardiac arrest that are reversed will be collected under this endpoint. If they are not reversed the event will be categorized as death.

Outcome 3: All-cause mortality at 1 year after randomization.

Outcome 4: A composite endpoint of all-cause mortality, MI, coronary revascularization, acute renal failure, or post-randomization stroke at 30 days after randomization.

Outcome 5: Length of hospital stay after randomization.

3.2.3. Tertiary Outcome Variables

Individual rates of the outcomes that consist of individual components of the primary endpoint

3.2.4. Safety Outcome Variables

Safety measures include serious adverse events and laboratory assessments.

4. STUDY METHODS

4.1. General Study Design

The study is a parallel, single-blind, controlled, superiority trial in which participants will be randomized to a restrictive or a liberal transfusion group. This study will randomize 1520 Veterans at 15 VA Medical Centers. The total recruitment period will be approximately 4 years which will be followed by a 3 month active and 9 month passive follow-up period. The duration of the study will be approximately 5 years. Consent for the study will be obtained prior to the index surgical intervention at the clinic visit or, in case of inpatients, at the hospital ward pre- or postoperatively. Randomization will be performed via a central telephone randomization system once the participant has a confirmed post-operative Hb < 10gm/dl. Active follow up will be up to three months after randomization. Passive follow up will be from 3 months to one year after randomization. The study flow is shown in Appendix 1. There will be no blinding at the treating physician level; however the participants and the Endpoint Committee will be unaware of group allocation.

Follow up forms will be filled out during two postoperative clinic visits that will be after the 30^{th} and 90^{th} post-randomization days. Participants who cannot make the clinic visits will be assessed by phone call follow-up, during which they will be asked specific questions to ascertain whether signs or symptoms related to any of the endpoints have developed. In

addition, the electronic medical record, will be assessed to collect relevant information. If a participant gets re-admitted at any time after discharge and within 90 days after randomization, the electronic medical record will be examined for the presence of any of the diagnoses that consist part of either the primary or any other endpoints. If the participant has been admitted to a non-VA facility, a full copy of hospital records from that admission will be obtained and assessed for the presence of any of the outcomes. History and physical, consultation notes and progress notes will all be reviewed. Furthermore, particular attention will be paid to laboratory reports for troponin, creatinine, CK-MB, and WBC levels, reports of cardiac echograms, radiology reports, and results of cultures (blood, wound, sputum). Participant agreement for release of information to the study personnel for all postoperative hospital visits that occur within 90 days after randomization will be obtained as part of the original consent form.

Assessment of one year mortality will be performed as part of a passive follow up performed by the Chairman's office via examination of the electronic medical record, follow up phone calls, and search of national databases documenting mortality.

4.2. Inclusion-Exclusion Criteria and General Study Population

All Veterans who are scheduled to undergo vascular or general surgery at a VAMC will be invited to participate in this trial. The inclusion and exclusion criteria are outlined below.

A. Inclusion Criteria

1) Male and female Veterans older than 18 years of age who have postoperative Hb < 10gm/dl within 15 days after the index operation
2) Patients undergo an operation in either one of the three following categories
    a. Veterans who undergo PAD – related operations including but not limited to the following: aortobifemoral or aortobiiliac bypass, open abdominal aortic aneurysm repair with simultaneous repair of aortoiliac occlusive disease, visceral bypass, iliofemoral bypass, femoral bypass or endarterectomy, infrainguinal bypass; thromboembolectomy; supra-aortic trunk bypass or endarterectomy, carotid endarterectomy, and major lower extremity amputations (transfemoral, through the knee, or transtibial)

b. Veterans with past medical history of ischemic stroke/TIA of likely carotid origin, or history of IHD (defined as known prior MI, EKG findings consistent with prior MI, prior percutaneous coronary intervention, prior coronary artery bypass surgery, history of angina for which the patient is currently receiving treatment, or stress test indicating myocardial ischemia), or history of PAD (defined as prior intervention for PAD or ABIs < 0.9) who undergo the following General Surgery operations: Open cholecystectomy or other open complex biliary reconstruction (such as open common bile duct exploration for stones, reconstruction as part of oncologic operations such as palliative pancreatic cancer procedures), open or laparoscopic small bowel resection, pancreatectomy, colon resection, colostomies (reversals and takedowns), intestinal anastomosis takedown and revision, rectal resection, splenectomy, transhiatal esophagectomy, liver resection, gastric operations (resections or repairs), gastric bypasses, adrenalectomy, major diaphragmatic hiatal hernia repair, Nissen fundoplications, and ventral hernia repair

c. Veterans with past medical history of ischemic stroke/TIA of likely carotid origin, or history of IHD, or history of PAD (defined as prior intervention for PAD or ABIs < 0.9) who undergo the following Vascular Surgery operations: Open aneurysm repair (including but not limited to carotid, subclavian, abdominal aortic, iliac, femoral, or popliteal aneurysms); and complex endovascular aneurysm repair (defined as fenestrated endograft, or endograft with need for iliac conduit, or endovascular aneurysm repair with simultaneous femoral artery reconstruction or bypass). Subclavian/vertebral bypasses and transpositions are eligible with a history of PAD/IHD/ischemic stroke.

B. Exclusion Criteria

1) Veteran unable to consent

2) Veteran unwilling to follow protocol (such as Jehovah's witnesses)

3) Veteran with known history of hereditary anemias such as Thalassemia or Sickle cell disease
4) Veteran with known history of hereditary bleeding disorders, such as factor VIII or factor IX deficiency
5) Veteran with prior history of adverse reaction to blood administration, such as fever, rash, or hemolysis
6) Veteran does not speak or understand English
7) Veteran hemodynamically unstable (systolic blood pressure <90 and heart rate >100 that persists for at least 30 minutes) or in cardiogenic shock for ≥ 48 hours after the index procedure
8) Veterans participating in another interventional trial
9) Pregnancy in female Veterans
10) Veteran is a prisoner or in custody of law enforcement
11) Prior randomization in the CSP#599
12) Patients who are known to have tested positive for COVID-19 and have not recovered prior to consent will not be consented. Any participant who is known to have a positive COVID-19 test during the screening process and has not recovered will be excluded prior to randomization.

Recovery from COVID-19 is defined as a patient who is asymptomatic (per local preoperative clearance policies) and at least 10 days post a positive test.

4.3. Randomization and Blinding

The clinical site coordinator will track the participants' postoperative Hb levels and identify participants whose Hb level is below 10 gm/dl and therefore eligible for randomization. iStat hemoglobin values may not be used as the basis for randomization/transfusion decisions. The CSPCC staff will prepare randomization schedules for each clinical site participating in the study. The study randomization to either liberal or restrictive transfusion policy will be done by an Interactive Touchtone Telephone Randomization System (ITTRS). A stratified block randomization scheme with block sizes of 2 and 4 will be used to randomize participants in the two transfusion groups. The stratifying factors are clinical site and revised cardiac risk index

(RCRI) class. The participants and the Endpoint Committee will be unaware of treatment group allocation.

4.4. Study Assessments Used in the Analysis

4.4.1. Baseline Assessment

Participants' demographics, medical history, physical exam, and medication use are collected. Baseline assessments will be collected the time between identification of an eligible participant and either randomization or 15 days after surgery (or until discharge, whatever comes first) including revised cardiac risk index (RCRI), patient history, hemoglobin level, ECG diagnosis, troponin, serum creatinine, albumin, and patient clinical status. Data collected during this period is used primarily for monitoring recruitment and randomization status. We will maintain the information of all identified potential participants. This will be accomplished by completing the screening form for every participant presenting to the clinical site for eligible operations including those who are excluded from the study for any reason. Following is a list of assessments that we plan on collecting:

Screening Record: To compare patient screened (but not randomized) to patient randomized in this study, a comprehensive screening assessment will be completed for all potentially eligible participants scheduled to receive a vascular/general surgery procedure at a participating center by the Study Coordinator.

Demographic and Contact Information: Following randomization, the clinical site coordinator will collect the demographic and participant information. The contact information will be used to assist with the collection of 30-day, 90-day and one year follow-up data. The demographic information will include participant's age, gender, race, marital status, etc.

Clinical Data: At the time of randomization, the site coordinator will also collect clinical data using information from the medical record and consultation with the surgeon as needed. These will include height, weight, most recent available preoperative serum Hb, albumin, blood pressure, and history of comorbidities, including coronary artery disease, end-stage renal disease, chronic obstructive pulmonary disease, hyperlipidemia, diabetes mellitus, and hypertension. To assure that MI or acute renal failure have not occurred prior to the time of randomization, the patient's chart will be reviewed for Troponin, ECG and serum Creatinine. If

these values are available in the 24 hours prior to randomization, they will not be collected again. If unavailable within this period, ECG, serum creatinine, and troponin data will be collected within 24 hours from the time of randomization.

We will also collect information on prior history of MI, coronary artery bypass, and stent placement. Furthermore, intraoperative assessments will be collected during the surgical procedure, such as type of operation, amount of intraoperative blood loss, intraoperative transfusion, amount and type of fluids administered, and length of the operation.

4.4.2. Follow-up Assessment

Follow-up assessments will be collected after participants discharged from hospital including 30- day and 90-day active follow-up assessments and one-year passive follow-up assessment.

Thirty Day Follow-up: Participants will be given an appointment for a clinic visit within (+/-) one week after the 30 post-randomization day. Questions regarding symptoms related to MI, other cardiac events, stroke, pneumonia, and wound infection will be asked. If a participant has a readmission prior to the 30-day post-randomization time point, then the electronic medical record, will be reviewed to determine whether the reason for admission includes any of the complications that consist of the primary or other study endpoints, such as coronary revascularization or acute renal failure. If the participant has been admitted to a non-VA hospital, then complete records from this admission will be obtained from that hospital to document the reason for admission and the development of study endpoints leading to readmission. The hospital records obtained will include History and Physical, all consultations, procedures, laboratory values, fluid cultures, copies of EKG and Echocardiography reports, as well as reports from all imaging studies performed, catheterization laboratory reports and operating room reports. To assure access to these records, release of information forms will be signed by the participant as part of the initial informed consent process. If the participant does not present for the follow up within two weeks from the anticipated appointment time, an electronic medical record review and phone call follow-up will be performed and focused questions will be asked, to identify the occurrence of any of the endpoints. Questions about interval readmission will also be asked at the follow up visit/call.

Ninety Day Follow-up: Participants will be given a clinic appointment within two weeks (+ only) after the 90th post-randomization day. Questions regarding symptoms related to cardiac events, stroke, infectious complications will be asked as described above for the 30-day post-randomization follow up. If participants are unable to make the clinic visit within two weeks of the assigned appointment then an electronic medical record review and phone call follow-up will be performed as described above. Readmissions since previous follow-up will also be investigated with similar series of actions as with the 30-day post-randomization follow-up. Pertinent laboratory values (creatinine, troponin), EKG results, cardiac catheterization reports and operating room reports since the previous visit will be reviewed in the electronic medical record to ascertain the presence of coronary revascularization, stroke, MI, or acute renal failure.

One Year Follow-up: Follow up will be performed by trained staff from the Chair's office at twelve months after randomization to ascertain vital status. The CSPCC will generate listings of participants due for follow-up which will be sent to the Chairman's personnel responsible for conducting the telephone interviews. Follow-up data will be obtained by study staff. This removes the need for personal identifying information to be maintained at the individual sites or the CSPCC and helps to protect participant confidentiality. Study participants will be called, chart reviews will be performed, and the VHA Death Ascertainment File (DAF) data will be used to determine a participant's death and date of death. The DAF will be used to assess the one-year vital status of those participants discharged alive from the hospital for whom vital status cannot be determined. Social Security number will be used to obtain the patient identifier PatientICN, which will be necessary for linkage to the DAF. The data collection schedule as shown in Appendix 2.

4.4.3. Safety Assessment

Given the large number of comorbidities expected in the study population and the high-risk operative procedures that these patients will be undergoing, it is anticipated that a large number of AEs will be observed, most of which will not be related to the study intervention. For this reason, the study will only collect reports of Serious Adverse Events (SAEs). Serious adverse events are defined by the ICH for Clinical Safety Data Management (ICH-E2A), the

Food and Drug administration (21CFR312.32) and CSP Global SOP 3.6, as any untoward medical occurrence that:

- Results in death,
- Is life threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly/birth defect, or
- Any other condition that, based upon medical judgment, may jeopardize the subject and require medical, surgical, behavioral, social or other intervention to prevent such an outcome.

SAEs will be identified and documented on the SAE CRF in appropriate medical terminology. The relationship of the SAE to the study intervention involves an assessment of the degree of causality (attributability) between the study intervention and the event. Site investigators will be asked to provide an assessment of relatedness. The assessment provided by the site investigator is part of the information used by the sponsor to determine if the adverse event presents a patient safety concern or requires regulatory reporting. Pursuant to CSP Global SOP 3.6.2, an AE or SAE is deemed to be associated with the use of a study drug/device if "there is a reasonable possibility that the experience may have been caused by the drug/device or by participation in the trial." Thus, all adverse events with a reasonable causal relationship to the investigational treatment should be considered "possibly related" or "related." A definite relationship does not need to be established but there must be some evidence to suggest a causal relationship between the investigational treatment and the adverse event (21 CFR 312.32). The following levels of relatedness will be used in this trial:

- Not attributed to a study intervention
- Possibly attributed to a study intervention
- Attributed to a study intervention.

All SAEs, whether related or unrelated to the treatment interventions, will be recorded and reported in an expedited fashion. Assessment of relatedness for SAEs is described above. Unexpected serious adverse events that are attributed or possibly attributed to a study intervention will be managed as provided in CSP Global SOP 3.6. Directions on how to

complete the Serious Adverse Event Form will be detailed in the Operations Manual. Sites are required to report each SAE to the Sponsor within 3 calendar days from the time the site investigator becomes aware of it. The PCC Study Pharmacist will complete a safety and regulatory review of all SAEs. All investigators will be notified of any new hazards or other trends involving patient safety as provided in Global SOP 5.3. Active monitoring of reportable SAEs will begin as soon as the participant is randomized and will continue until the participant's 90th post-randomization day. The treatment plan includes follow-up outpatient visits of all patients for 3 months after randomization.

4.5. Sample Size Consideration

The sample size estimation and power analysis are based on the hypothesis testing of the primary composite endpoint of all-cause post-randomization mortality, myocardial infarction (MI), coronary revascularization, acute renal failure, or post-randomization stroke up to 90 days after randomization. The primary hypothesis of the study is that in VA patients with high cardiac risk undergoing a surgical procedure, a significantly smaller proportion of participants receiving blood under a liberal transfusion strategy will experience the composite endpoint compared to participants under restrictive transfusion strategy at 90 days after randomization. The primary analysis will be done as an "intent-to-treat" analysis. Our database review revealed that 29.8% out of 25,343 patients in the VA population who were at high cardiac risk and had nadir postoperative Hb range between 6-9 gm/dl developed the composite endpoint of death, MI, acute renal failure, or coronary revascularization within 90 days from the index operation. Based on the analysis, a baseline event rate of 30% for the composite endpoint is expected in the restrictive group. We also assume a 25% reduction or 22.5% event rate in the liberal group. To detect the expected 7.5 percentage point difference or 25% reduction, a sample size of 1444 will be required at 90% power, 5% type-I error rate and with a two-sided test (Appendix 3). Assuming 5% dropout rate, then 1520 participants (or 760/group) will be needed to achieve the desired testing power.

5. GENERAL ANALYSIS CONSIDERATIONS

5.1. Timing of Analysis

The Study Group, which consists of all participating investigators and study coordinators, will meet annually to discuss the progress of the study and any problems encountered during the conduct of the trial. This group will be provided a report prior to meetings. The information provided will include data on:

- Screening, Enrollment, and Retention
- Participant background characteristics at entry
- Data quality and protocol adherence

The groups charged with monitoring the various aspects of the study will be the Executive Committee, the Data Monitoring Committee (DMC), and the VA's Central IRB. These committees will meet at regular intervals according to the current Cooperative Studies Program guidelines: prior to the beginning of participant intake and at least every twelve months thereafter.

The final analysis will be performed after the data collection phase of the study is complete and the data are cleaned and locked per CSP SOPs and after the finalization and approval of this SAP document.

5.2. Missing Data and Imputations

Every effort will be made to minimize the occurrence of missing data, particularly for the primary and main secondary outcome measures. For the primary outcome, every effort will be made to contact participants until subject termination. In the event of a potential drop out, every effort will be made to capture the primary outcome data from the VA databases. For participants who drop out during the study multiple imputation (MI) method may be used for certain endpoint analyses. Multiple imputations will be based on Rubin's procedure using SAS PROC MI and PROC MIANALYZE when missing is at random. Sensitivity analysis will be performed to compare the results from the imputed data and the complete data without imputation.

5.3. Analysis Conventions

This section details general policies to be used for the statistical analyses. Departures from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the specific section take precedence over the general policies. The following policies will be applied to all data presentations and analyses.

All statistical tests will use a significance level of $\alpha = 0.05$ unless otherwise specified. Two-tailed tests will be performed for all analyses that use statistical testing.

All p-values will be rounded to 3 decimal places. All p-values that round to 0.000 will be presented as '<0.001' and p-values that round to 1.000 will be presented as '>0.999'. Any p-value $\leq \alpha$ will be considered statistically significant.

Summary statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean, median, standard deviation (SD), minimum, and maximum for continuous variables.

All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value.

All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. The decimal of the percentage may be dropped due to space constraints when creating a table.

All listings will be sorted for presentation in order of intervention group, site number, subject number, and date of procedure or event.

All analysis and summary tables will have the population sample size for each intervention group in the column heading.

Calculating change from baseline to a visit will be done as follows: change = visit – baseline.

Unless otherwise specified, baseline is defined as the last data point before the participant is randomized.

Version 9.4 of SAS® or higher will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.

Updated version of MedDRA will be used for adverse event and pre-intervention coding.

5.4. Analysis Populations

Intent-to-Treat (ITT) – This population is defined as the population of participants (except non-Veterans and previous participants of this trial) who will be randomized to either of the transfusion strategy groups – Liberal or Restrictive. The participants will be categorized (in terms of their transfusion strategy assignment) based on their initial randomized group and will be included in analyses irrespective of their status – completer or drop out of the study before completion. The testing power for the primary endpoint is estimated as 90% in this population.

Modified Intent-to-Treat (mITT) – This population is defined as a subset of the ITT population that excludes randomized participants in a justified way, i.e., participants who are found to be ineligible (violating inclusion/exclusion criteria) or participating in more than one simultaneous intervention trial.

No-Recent-Transfusion – This population is defined as a subset of the ITT population excluding the participants who will receive transfusions within 30 days prior to or during the index operation, or after the index operation but before randomization.

Completers – This population includes all ITT participants who will complete all protocol-required lab and EKG assessments, hemoglobin monitoring and transfusion records in the hospital stay or until death, as well as completing assessments of the 5 individual components of the primary endpoint at 30 day and 90-day follow-up or until death.

Per Protocol – This population includes all ITT participants who will adhere to transfusion protocol in their assigned intervention groups.

Safety – This population includes all participants (except non-Veterans and previous participants of this trial) who will be randomized to either of the transfusion strategy groups – Liberal or Restrictive.

5.5. Interim Analysis and Data Monitoring

5.5.1. Data Monitoring Committee

The Data Monitoring Committee (DMC) will review the progress of the study and will monitor participant intake, outcomes, adverse events, and other issues related to participant safety. The DMC makes recommendations to the Director of the Clinical Science Research and Development (CSRD) Service about whether the study should continue or be stopped. The DMC will consider safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or the unfeasibility of addressing the study hypothesis (e.g., poor participant intake, poor adherence to the protocol). In general, this committee meets at six to nine months after the start of subject recruitment and yearly thereafter. The committee will receive reports about two weeks prior to their annual meetings and at six monthly intervals in between the annual meetings.

5.5.2. Planned Schedule of Interim Analysis and Stopping Rules

There will be three interim analyses of the primary outcome measure performed in the study when 25%, 50%, 75% of the planned participants completed their participation in the study. If analysis of the primary outcome rates at the time of interim analysis indicates that the null hypothesis can be rejected the study will be recommended for termination for safety reasons. A Haybittle-Peto interim analysis is proposed where a Z-statistic is computed and if it should exceed the critical value of 4.0 then the committee should recognize that an important "warning" has been made and that a decision is indicated (Appendix 4).

6. SUMMARY OF STUDY DATA

6.1. Subject Disposition

Subject disposition will be summarized for all participants that signed the consent form and for the ITT population. The following data will be presented:

- A CONSORT diagram including the overall number of screened, eligible, consented, and randomized (Figure 1).
- A figure of participants randomized and expected by month (Figure 2).
- Summary of screening, consenting, and randomization by site (Table 1).
- Reasons of ineligibility for consent and consent information by site (Table 2)

- Reasons of ineligibility for randomization by site (Table 3).
- Reasons of eligible participants not randomized by site (Table 4).
- Participant disposition by sites for all randomized participants (Table 5).
- Participant disposition by intervention group for all randomized participants (Table 6) .
- A list of participants who are administratively terminated (Table 6.1).
- A list of participants whose termination reasons are listed as 'Other' (Table 6.2).

6.2. Study Adherence

The following tables will be presented:

- Summary of protocol deviations by intervention (Table 7).
- Summary of approved transfusion protocol halting by site (Table 8).
- Summary of transfusion-related protocol deviations by site (Table 9).

6.3. Subject Demographics

Subject demographics will be summarized by intervention group, and for all participants (ITT and mITT; Tables 10a-b). The subject demographics such as age, race, gender, ethnicity, will be analyzed. For continuous variables, the sample size, mean/SD or median/interquartile range, minimum, and maximum values will be calculated and the difference between the intervention groups will be tested either by Student t or Wilcoxon rank sum test depending on data distributions. For categorical variables, the number and percentage of participants by center or the intervention group will be tabulated and the difference between the intervention groups will tested using Pearson chi-square test.

Age will be calculated as the number of years between the participant's birth date and randomization date.

6.4. Baseline Characteristics

Baseline comparability among the intervention groups will be evaluated with respect to baseline characteristics including height, weight, BMI, pre-operative hemoglobin, albumin, creatinine, SBP/DBP, RCRI class besides the demographic variables including BMI. The

sample size, mean, median, SD, minimum, and maximum values for the continuous measures and the number and percentage for the categorical variables will be summarized for each intervention group and all participants (Tables 11a-b).

Weight at screening from physical examination CRF will be used for the summary.

BMI = (Weight/Height^2)*100^2. The unit of weight will be kilogram and the unit of height will be centimeter.

6.5. Medical History

The number and percentage of participants reporting a medical history will be summarized by the following medical conditions: Hypertension, hyperlipidemia, coronary artery disease, congestive heart failure, COPD or previous active TB, dementia or current change in mental status, MI within 6 months, malnourished or cachectic, cancer or current chemotherapy, immunodeficiency or infection with HIV, ischemic stroke or TIA, prior coronary stent, cardiac arrhythmias, MI older than 6 months, end stage renal disease, prior coronary bypass, diabetes treated with medications (oral hypoglycemic or insulin), past smoking, and current smoking (Tables 12a-b).

6.6. Pre-admission Ambulation and Residence

The number and percentage of participants in each pre-admission ambulation category and residence status will be summarized as in Tables 13a-b.

6.7. Pre/Post-Admission Medications

Pre/after admission medications are recorded in this study. Each summary below will be done for each intervention group and for all participants:

- Prior medications – Prior medications are collected for those randomized patients before their admission (Tables 14a-b)
- Current medications – Current medications are medical orders for those randomized patients during their hospital stay at the day before the index operation, operation day, the day after the operation, two days after the operation, and discharge day. The

number and percentage of participants who are prescribed these medications on each of the above days will be summarized (Tables 15a-b).

7. EFFICACY ANALYSES

The primary analysis of the study will be performed on the primary endpoint on the ITT population. The secondary analyses will be performed on the secondary and tertiary endpoints on the ITT population, as well as the analyses performed on all the primary, secondary, and tertiary endpoints on the mITT, No-Recent-Transfusion, Completers, and Per Protocol populations unless otherwise specified. Potential difficulties of convergence of model fit, which may arise in efficacy analyses that include covariates, will be handled using the method described in Section 7.1.

7.1. Primary Endpoint Analysis

The primary study endpoint will be a composite outcome of all-cause mortality, MI, coronary revascularization, acute renal failure, or post-randomization stroke within 90 days from randomization. A clinical events committee will adjudicate all component events for the primary endpoint. The number and percentage of participants with the composite endpoint at the 90-day visit after the randomization will be summarized and compared according to assigned transfusion strategy (analysis by intent to treat) using Pearson χ^2 test. Another analysis will compare primary endpoint between the two transfusion strategies stratified by clinical sites using the Cochran-Mantel-Haenszel test (Table 16a-e). The test for differences between transfusion strategies in the primary outcome will be conducted at an overall α-level of 0.05. Additional analysis will be conducted using logistic models to adjust for other clinical factors, such as age, RCRI, and nadir Hb. The interactions of the intervention with age, RCRI and nadir Hb will also be considered.

Odds ratio and 95% confidence interval (CI) will be presented using SAS PROC GENMOD or PROC LOGISTIC. Assumptions of the model including linearity in the logit of the composite event risk for continuous variables will be checked. We will assess goodness-of-fit using the statistic -2 log likelihood, which has a chi-square distribution under the null hypothesis that all the explanatory variables in the model are not associated with the outcome

variable. We will also consider the Akaike Information Criterion statistic and the Schwartz Criterion statistic, both of which adjust the -2 log likelihood for the number of items in the model. Models that show lack of fit will be reconsidered for the inclusion of additional variables or use of alternate models with assumptions that are better met by the study data. One alternate model if the model fit is poor for logistic regression is a log-linear model. For logistic regression analysis, if the coefficient for intervention effect is significant (i.e., the confidence interval for the odds ratio does not include 1), then the null hypothesis of no intervention effect adjusting for other covariates in the final model will be rejected. The P value for testing each covariate coefficient in the model being zero will be based on Wald test (Table 17a-e). The primary analysis will be done in the ITT population. Additional analyses will be done in the mITT, No-Recent-Transfusion, Completers, and Per Protocol populations.

7.2. Secondary Endpoint Analyses

Secondary endpoints included in the analysis are composite endpoints of post-randomization infectious complications (wound infections, pneumonia, and sepsis) at 90 days and cardiac complications (new cardiac arrhythmia, new or worsening CHF, and cardiac arrest not leading to death) at 90 days, all-cause mortality at one year after randomization, a composite endpoint of all-cause mortality, MI, coronary revascularization, acute renal failure, or post-randomization ischemic stroke at 30 days, and length of hospital stay after randomization.

For the binary endpoints, the effect of transfusion strategy on these endpoints will be analyzed initially with a Pearson chi-square test (Tables 18a-e) and additional analysis will be performed by taking account of age, RCRI, and nadir Hb using logistic regressions (Tables 19a-e), as described in the primary endpoint analysis.

For the length of hospital stay after randomization, medians (interquartile ranges) will be presented, and Wilcoxon rank sum test will be used to compare the medians of the length of hospital stay between the two intervention groups (Tables 20a-e) using PROC NPAR1WAY. In addition, quantile regression model will be performed using PROC QUANTREG to test the effect of the intervention on the time until discharge from hospital adjusted for age, RCRI, and nadir Hb (Tables 21a-e), as described in the primary analysis. The test for differences between transfusion strategies in each secondary outcome will be conducted at an α-level of 0.01. The

analyses will be done in the ITT, mITT, No-Recent-Transfusion, Completers, and Per Protocol populations.

7.3. Tertiary endpoint Analyses

Tertiary endpoints included in the analysis are individual components of the primary composite outcome of all-cause mortality, MI, coronary revascularization, acute renal failure, or post-randomization stroke at 90 days. All are considered as binary variables in the study, and the effect of transfusion strategy on these endpoints will be analyzed initially with a Pearson chi-square test (Tables 22a-e). The test for differences between transfusion strategies in each tertiary outcome will be conducted at an α-level of 0.01. Additional analyses will be carried out by taking account of age, RCRI, and nadir Hb using logistic regressions (Tables 23a-e), as stated in the secondary endpoint analyses. The analyses will be done in the ITT, mITT, No-Recent-Transfusion, Completers, and Per Protocol populations.

7.4. Other Analyses

Age of blood in relation to 90-day composite endpoint, wound infection, and pneumonia

Analyses will be conducted of the associations between characteristics of transfused blood and three outcome measures: 90-day composite endpoint (Tables 24a-e), wound infection (Tables 25a-e) , and pneumonia (Tables 26a-e). Current data collection plans call for blood expiration dates and the age of each unit of blood transfused will be calculated. Logistic regression models will be fitted to test for association between these outcomes and age of blood transfused (entered in different models as oldest unit transfused or as mean age of all units transfused). The analyses will be adjusted for baseline age, RCRI, nadir Hb, and the transfusion intervention. The test for differences of these outcomes will be conducted at an α-level of 0.05 for the primary outcome and 0.01 for wound infection and pneumonia. The analyses will be done in the ITT, mITT, No-Recent-Transfusion, Completers, and Per Protocol populations.

Time-to-event analysis for primary and major secondary endpoints

Survival analysis techniques will be used to analyze the time-to-event data for the primary and major secondary endpoints. Kaplan-Meier method will be used to estimate the survival (not experiencing event) over time in the two intervention groups and a log-rank test

will be used to compare the survival functions in the two groups for the primary endpoint and the secondary endpoints using PROC LIFETEST. Cox's Proportional Hazards models will be used to test the effect of the intervention on the time until endpoint events adjusted for age, RCRI, and nadir Hb, as described in the primary endpoint (Tables 27a-e, with an α-level of 0.05), and secondary endpoint (Tables 28a-e, with an α-level of 0.01) analyses using PROC PHREG. The analyses will be done in the ITT, mITT, No-Recent-Transfusion, Completers, and Per Protocol populations.

8. SAFETY ANALYSES

All safety analyses will be done for the safety population and reported in tabular forms. These analyses include serious adverse events and laboratory measurements.

8.1. Serious Adverse Events

Serious adverse events (SAEs) are defined by the ICH for Clinical Safety Data Management (ICH-E2A), the Food and Drug administration (21CFR312.32) and CSP Global SOP 3.6, as described in the section 4.4.3. Incidence of SAEs will be summarized for each intervention group by body system and MedDRA term. The number and percentage of participants with each body system and MedDRA term will be presented for each intervention group (Table 29). A list of SAEs where deaths of randomized participants are indicated will be created (Table 30).

8.2. Laboratory Measurements

Laboratory measurements including Hemoglobin (gm/dl), Troponin (ng/ml), and Creatinine (mg/dl) are measured during the participants hospital stay. For each measurement, the sample size, median, lower quartile, upper quantile, minimum, and maximum values for the daily lowest value of each lab variable on randomization day, post-randomization Days 1, 2, 3, 4, 7 and discharge day in each intervention group will be presented (Table 31).

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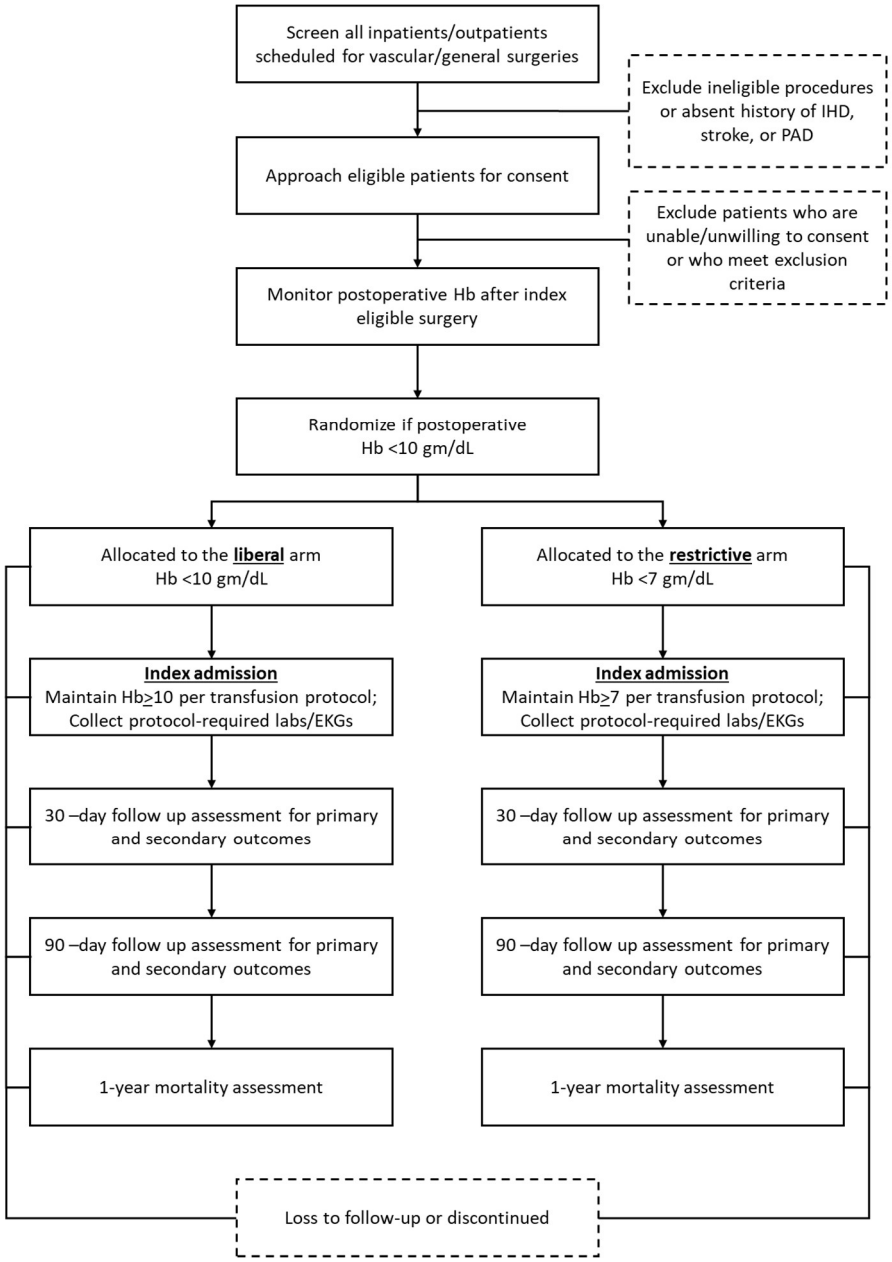
APPENDICES

Appendix 1. Study Flow



Appendix 2. Data Collection Schedule

599	Pre-Randomization			Post-Op Day 1-15	Post-Randomization Days									Follow-Up		
	Pre-Screening													Post-Randomization Day +		
Assessments	Pre-Op	Consent	Index Operation		Randomization Day 0	R-Day 1	R-Day 2	R-Day 3	R-Day 4	R-Day 5	R-Day 6	R-Day 7	Additional	Discharge	30 Days (±7 days)	90 Days (+14 days)	1 Year
Fm 86 Consent Confirmation		R															
Fm 1 Consent Randomization	p1	T(p2,3)	T	T	R(p4,5)												
Fm 2 Participant History/Clinical Data														R**			
Fm 3 Hemoglobin					R	R	R	R	R	A	A	R	A****	RA			
Fm 4 Transfusion Record					A	A	A	A	A	A	A	A	A	A			
Fm 6 Laboratory Markers***					R	R	R	R	R	A	A	R		R***			
Fm 7 Patient Status															R	R	
Fm 8 MI Confirmation															A	A	
Fm 9 Infect/Cardiac Complications															R	R	
Fm 10 Participant Status at 1 Year*																	R*
Fm 11 SAE	From Randomization +90 days or Termination																
Fm 12 SAE Follow Up	Follow-up SAE every 30 Days until resolution, stabilization, PR +90 days or Termination															RpS	
Fm 13 Protocol Deviation		A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Fm 14 Participant Termination*****					A	A	A	A	A	A	A	A	A	A	A	R	
Fm 19 COVID-19 Exclusion Criteria#	R	R												R			

	Post-Operation					
	Day -1	Day 0	Day 1	Day 2	Day 3+	Discharge
Fm 5 Medical Orders	E	E	E	E		R

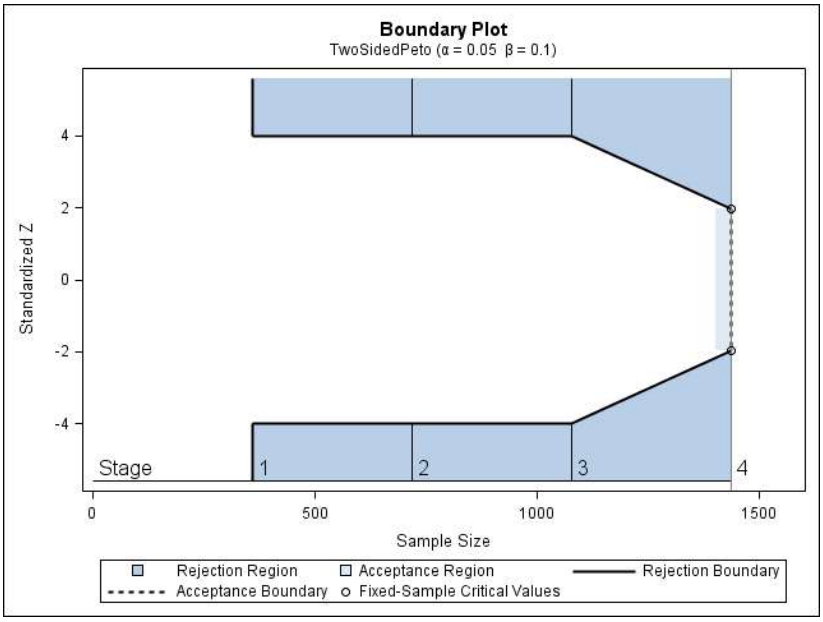
Note: *Chairman's office use only; Related time periods; A = if Actionable; E = Req. Form Entry if Randomized; R=Req. entry/complete form; RpS=Req. per SAE; T=Data req. even if not randomized; PR=Post-randomization; D/C=discharge; RA=Hb collectedPR Day 0-4,7 and/or D/C and according to ****standard clinical practice; **Req. if eligible but not randomized; ***Labs are collected PR Day 0-4, 7 and/or D/C (if PR day before Day 7); ECGs are collected PR Day 0, 1 & 4 or D/C if D/C is before Day 4; ***** Only one Form 14 req per participant. p1= Pre-Op use Form 1 Page 1. t(p2.3)=Once consented consider form 1: pages 2 & 3 part of pre-screening. R(p4,5)=If Randomized use Form 1: page 4 & 5. # See Form 19 for details.

PROTOCOL Version 6
Image Version 11/30/2021

Appendix 3. Power Analysis

90 Day Composite Endpoint (%)				Power (%)			
Liberal	**Restrictive**	**Difference**	**Percent Difference**	**75**	**80**	**85**	**90**
17.50	25.00	7.50	30.0	826	932	1066	1248
18.75	25.00	6.25	25.0	1214	1372	1570	1836
20.00	25.00	5.00	20.0	1936	2188	2502	2928
21.00	30.00	9.00	30.0	650	734	840	982
22.50	**30.00**	**7.50**	**25.0**	**954**	**1080**	**1234**	**1444**
24.00	30.00	6.00	20.0	1520	1718	1964	2298
24.50	35.00	10.50	30.0	526	594	678	794
26.25	35.00	8.75	25.0	770	870	994	1164
28.00	35.00	7.00	20.0	1222	1382	1580	1848

Appendix 4. Haybittle-Peto Interim Accept/Reject Boundary



Appendix 5. Tables and Figures for Data Presentation

Figure 1. Study Recruitment Consort Flow Diagram

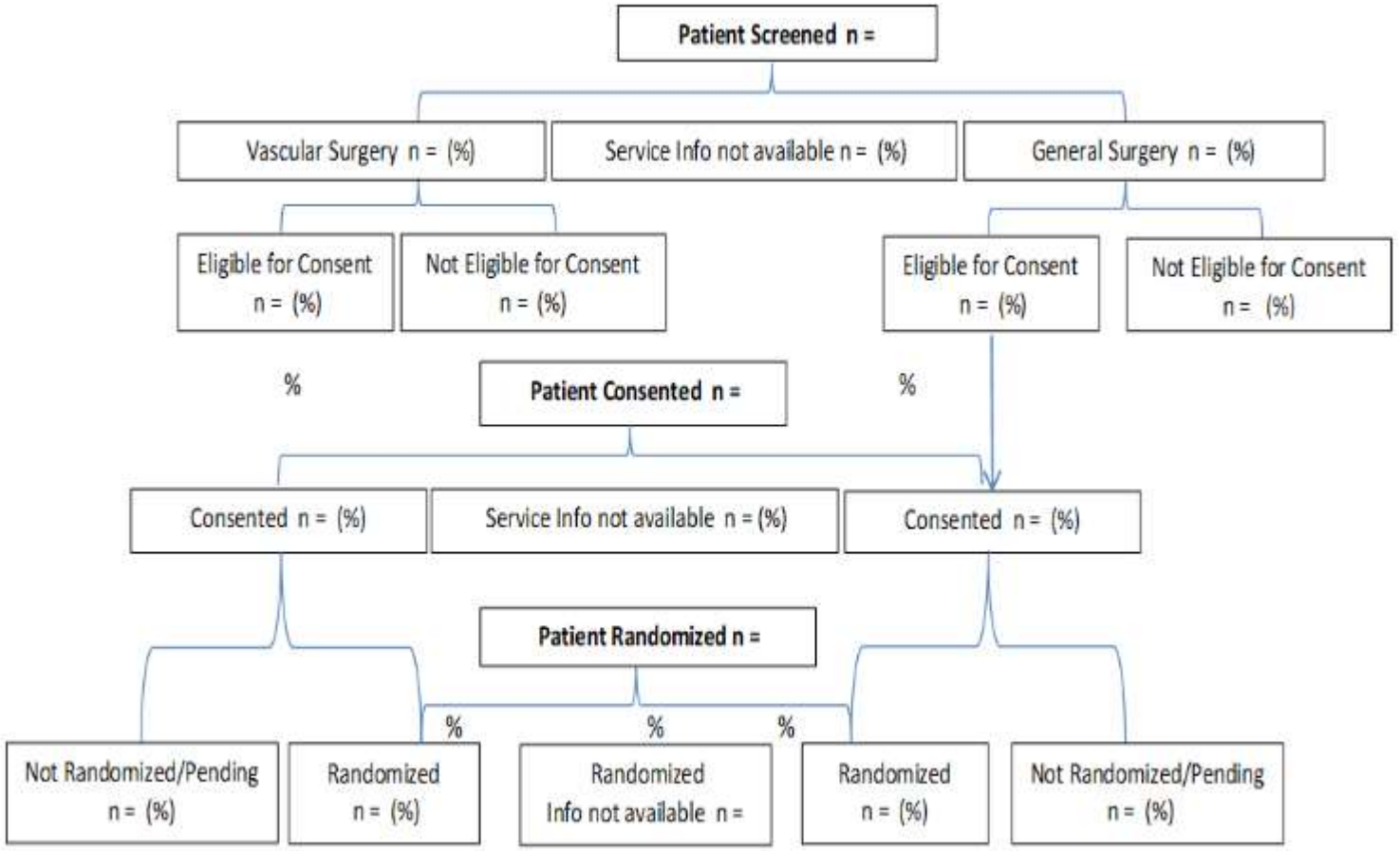


Figure 2. Number of Participants Randomized vs Expected

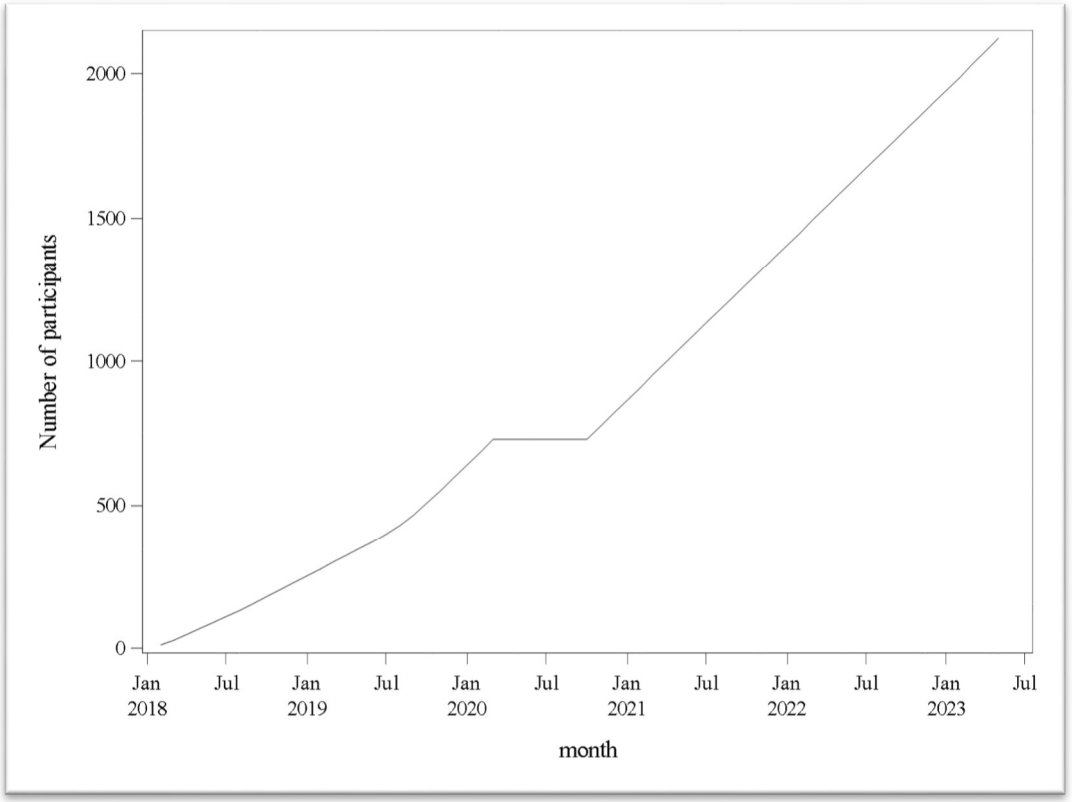


Table 1. Summary of Screening, Consenting, and Randomization by Site

Categories	Buffalo	Cleveland	Dallas	Gaines-ville	Houston	Little Rock	Port-land	Tampa	Loma Linda	Minne-apolis	Ashe-ville	Palo Alto	Pitts-burg	San Fran	Seattle	Long Beach	Total
Number of Subjects Screened																	
Number of Subjects Excluded for Consent																	
Ineligible for Consent																	
Unable to Consent																	
Unable and/or Unwilling to Follow Protocol																	
Number of Subjects Consented																	
Percent of Subjects Consented (over Eligible for Consent)																	
Number of Subjects Excluded for Randomization																	
Ineligible for Randomization																	
Eligible for Randomization, but Not Randomized																	
Number of Subjects Randomized																	
Percent of Subjects Randomized (over Eligible for Randomization)																	

Table 2. Reasons of Ineligibility for Consent and Consent Information by Site

Categories	Buffalo	Cleveland	Dallas	Gaines-ville	Houston	Little Rock	Port-land	Tampa	Loma Linda	Minne-apolis	Ashe-ville	Palo Alto	Pitts-burgh	San Fran	Seattle	Long Beach	Total
Veterans Screened																	
Not Veteran age 18 years or older																	
No Eligible Operation, no																	

history of CVD, IHD, or PAD																	
No Eligible Operation, with history of CVD																	
No Eligible Operation, with history of IHD																	
No Eligible Operation, with history of PAD																	
No Eligible Operation, with history of CVD and IHD																	
No Eligible Operation, with history of CVD and PAD																	
No Eligible Operation, with history of IHD and PAD																	
No Eligible Operation, with history of CVD, IHD, and PAD																	
Eligible General Operation, no history of CVD, IHD, or PAD																	
Eligible Vascular Operation, no history of CVD, IHD, or PAD																	
COVID-19 Positive During Pre-Screening																	
Veterans Ineligible for Consent (% over Screened)																	

Veterans Eligible for Consent (% over Screened)																	
Veteran unable to consent (% over Screened)																	
Veteran unable and/or unwilling to follow protocol (% over Screened)																	
Veterans Consented (% over Eligible)																	

Table 3. Reasons of Ineligibility for Randomization by Site

Categories	**Buffalo**	**Cleveland**	**Dallas**	**Gaines-ville**	**Houston**	**Little Rock**	**Port-land**	**Tampa**	**Loma Linda**	**Minne-apolis**	**Ashe-ville**	**Palo Alto**	**Pitts-burgh**	**San Fran**	**Seattle**	**Long Beach**	**Total**
12. Veteran with known history of hereditary anemias (% over Consented)																	
13. Veteran with known history of hereditary bleeding disorders (% over Consented)																	
14. Veteran with prior history of adverse reaction to blood administration (% over Consented)																	
15. Hemodynamically unstable or in cardiogenic shock																	

(% over Consented)																	
16. Veteran participating in another interventional trial (% over Consented)																	
17. Veteran is a prisoner or in custody of law enforcement (% over Consented)																	
18. Prior randomization in CSP #599 (% over Screened)																	
19. Pregnancy in female Veterans (% over Consented)																	
22. RCRI Class not available (% over Eligible for Randomization)																	
23. Index surgery not performed as planned (% over Screened)																	
24. Hb did not go below 10gm/dl within 15 days (% over Screened)																	
COVID-19 Positive After Consent but Before Randomization																	
Number of Participants ineligible for randomization (% over Total Consented)																	
Number of eligible																	

Participants randomized																	
Number of eligible Participants randomized (% over Total Screened)																	
Number of eligible Participants randomized (% over Total Consented)																	
Number of eligible Participants randomized (% over Total Eligible)																	

Table 4. Reasons of Eligible Participants Not Randomized by Site

Categories	**Buffalo**	**Cleveland**	**Dallas**	**Gaines-ville**	**Houston**	**Little Rock**	**Port-land**	**Tampa**	**Loma Linda**	**Minne-apolis**	**Ashe-ville**	**Palo Alto**	**Pitts-burgh**	**San Fran**	**Seattle**	**Long Beach**	**Total**
Number of Participants Eligible for Randomization who were NOT Randomized																	
Eligibility status changes (e.g., died, treatment plan changed, etc.)																	
Participant changed mind after consent signed																	
Investigator/Surgeon changed mind after participant signed consent																	

Site surgeon concerned about resources needed for on-site follow-up (cost, time, etc.)																		
No reliable method of follow-up contact with the participant (e.g., no phone, etc.)																		
Primary reason participant preferred non-enrollment																		
Primary reason surgeon preferred non-enrollment																		
- Surgeon prefers restrictive transfusion for participant																		
- Surgeon prefers liberal transfusion for participant																		
- Surgeon believes participant has too short of life expectancy to be included																		
- Surgeon believes participant is too high of a medical risk to be included																		
- Reason other than transfusion preference																		
Other Reason																		

Table 5. Participant Disposition by Sites for All Randomized Participants (ITT)

Status	**Buffalo**	**Cleveland**	**Dallas**	**Gaines-ville**	**Houston**	**Little Rock**	**Port-land**	**Tampa**	**Loma Linda**	**Minne-apolis**	**Ashe-ville**	**Palo Alto**	**Pitts-burgh**	**San Fran**	**Seattle**	**Long Beach**	**Total**

Participant Study Status - Randomized Ppts																	
Completed																	
Discontinued																	
Reason for Termination																	
Participant completed study																	
Participant voluntarily withdrew																	
Participant lost to follow-up (location unknown)																	
Participant became pregnant																	
Participant was incarcerated																	
Administrative termination (e.g., non-compliance)																	
Participant relocated																	
Other																	
SAE other than death																	
Participant died																	

Table 6. Participant Disposition by Intervention Group for All Randomized Participants (ITT)

Status		Liberal	Restrictive	Total
Participant Study Status - Randomized Ppts	n			
Completed	n (%)			
Discontinued	n (%)			
Reason for Termination	n			
Participant completed study	n (%)			
Participant voluntarily withdrew	n (%)			
Participant lost to follow-up (location unknown)	n (%)			
Participant became pregnant	n (%)			
Participant was incarcerated	n (%)			
Administrative termination (e.g., non-compliance)	n (%)			
Participant relocated	n (%)			
Other	n (%)			
SAE other than death	n (%)			
Participant died	n (%)			

Table 6.1. List of Participants Who Are Administratively Terminated

Center number	Participant ID number	Group	Termination Date	Details

Table 6.2. List of Participants Whose Termination Reasons Are Listed As 'Other'

Center number	Participant ID number	Group	Termination Date	Reason Termination

Table 7. Summary of Protocol Deviations by Intervention and Overall

Type		**Liberal (n=)**	**Restrictive (n=)**	**Total (n=)**
Total Number of Deviations	n			
SAE not reported	n (%)			
SAE reported late or SAE Follow-Up reported late	n (%)			
Did not follow instructions from IRB or other review bodies/committees	n (%)			
Confidentiality or privacy breach	n (%)			
Loss of source documents/samples/source media	n (%)			
Ineligible participant enrolled	n (%)			
Participant in more than one simultaneous interventional trial	n (%)			
Informed Consent/HIPAA documentation completed incorrectly	n (%)			
Informed Consent/HIPAA documentation is incomplete	n (%)			
Informed Consent/HIPAA not obtained prior to study procedures	n (%)			
Used incorrect informed consent/HIPAA version	n (%)			

Required study procedure not performed per protocol	n (%)			
Study activities performed by inappropriate personnel	n (%)			
Other (specify under Details of deviation)	n (%)			
Participant assigned to restrictive group was transfused with Hb above 7gm/dL	n (%)			
Participant assigned to liberal group was NOT transfused when Hb below 10gm/dL	n (%)			
Evidence of willful or knowing misconduct on the part of the study team	n (%)			
Participant repeated deviation with study requirements	n (%)			
Visit 30/90 outside of window	n (%)			
Transfusion outside of window/late	n (%)			
Labs/EKG on form 6 required for this date but not done	n (%)			
Hb on Form 3 required for date but not done	n (%)			
Hb used for Randomization trigger had batch draw time recorded outside of eligibility window but actual draw time was within eligibility window	n (%)			
Hb done after Randomization had batch draw time recorded outside of required window but actual draw time was within window	n (%)			
Transfusion Protocol deviation not covered by other Transfusion-specific Deviation Codes	n (%)			

Table 8. Approved Transfusion Protocol Halting by Site

	Buffalo	Cleveland	Dallas	Gaines-ville	Houston	Little Rock	Port-land	Tampa	Loma Linda	Minne-apolis	Ashe-ville	Palo Alto	Pitts-burgh	San Fran	Seattle	Long Beach	Total
1. Rapidly Bleeding (Form 4 Q9)(% over # Form 4 submitted)																	
2. Adverse Reaction During Transfusion (Form 4 Q10)(% over # Form 4 submitted)																	
3. Transfusion protocol stopped after MI; participant was transfused per attending (Form 8 Q3)(% over # Form 8 submitted)																	
4. Transfusion protocol continued after MI (Form 8 Q3)(% over # Form 8 submitted)																	
Sum of rows 1-3																	

(% over # Form 4 submitted)																	
Ppts with >=1 event in rows 1-3 (% over # Ppts with >=1 Form 4 submitted)																	

Table 9. Summary of Transfusion-Related Protocol Deviations by Site

	Buffalo	**Cleveland**	**Dallas**	**Gaines-ville**	**Houston**	**Little Rock**	**Port-land**	**Tampa**	**Loma Linda**	**Minne-apolis**	**Ashe-ville**	**Palo Alto**	**Pitts-burgh**	**San Fran**	**Seattle**	**Long Beach**	**Total**
# of Participants Randomized																	
# of Transfused Units																	
# Transfusion Deviations																	
Transfusion did or did not occur per randomization group Hb threshold																	
Transfusion occurred outside of protocol required window/late																	
Other transfusion deviation not covered by above																	
# of																	

Transfusion Deviations / # of Transfused Units																	
Transfusion did or did not occur per randomization group Hb threshold																	
Transfusion occurred outside of protocol required window/late																	
Other transfusion deviation not covered by above																	
# of Participants with Transfusion Deviations																	
Transfusion did or did not occur per randomization group Hb threshold																	
Transfusion occurred outside of protocol required window/late																	
Other transfusion deviation not covered by above																	
# of Participants with																	

Transfusion Deviations / # Randomized Participants																	
Transfusion did or did not occur per randomization group Hb threshold																	
Transfusion occurred outside of protocol required window/late																	
Other transfusion deviation not covered by above																	

Note: Transfusion did or did not occur per randomization group Hb threshold - Participant assigned to restrictive group was transfused with Hb above 7gm/dL, or participant assigned to liberal group was NOT transfused when Hb below 10gm/dL; Other transfusion deviation not covered by above - Transfusion Protocol deviation not covered by other transfusion-specific deviation codes.

Table 10a-b. Summary of Demographics (ITT, mITT)

Status	Statistics	Liberal Arm (N =)	Restrictive Arm (N =)	Total (N=)	p-value
Age (years) at consent	n				
	Mean (SD)				
	Median				
	Min, Max				
Sex	n				
Male	n (%)				
Female	n (%)				
Ethnicity	n				
Hispanic or Latino	n (%)				
Non-Hispanic or Latino	n (%)				
Unknown	n (%)				
Race	n				
American Indian or Alaska Native	n (%)				

Status	Statistics	Liberal Arm (N =)	Restrictive Arm (N =)	Total (N=)	p-value
Asian	n (%)				
Black or African-American	n (%)				
Caucasian	n (%)				
Native Hawaiian or Pacific Islander	n (%)				
Other	n (%)				
Unknown	n (%)				
Marital Status	n				
Married/Civil Union/Partnership	n (%)				
Never Married	n (%)				
Co-habitating	n (%)				
Divorced	n (%)				
Widowed	n (%)				
Separated	n (%)				
Military Service Branch	n				
Army	n (%)				
Air Force	n (%)				
Coast Guard	n (%)				
National Guard	n (%)				
Navy	n (%)				
Marines	n (%)				
Merchant Marine	n				
Military Service History	n (%)				
World War I	n (%)				
World War II	n (%)				
Korean conflict	n (%)				
Vietnam conflict	n (%)				
Gulf War	n (%)				
Balkan conflict	n (%)				
Afghanistan conflict	n (%)				
Iraq conflict	n (%)				
Peace time	n (%)				
Other	n (%)				

Table 11a-b. Summary of Baseline Assessment (ITT, mITT)

Assessments	Statistics	Liberal Arm (n = ?)	Restricted Arm (n = ?)	All Subjects (N = ?)
Height	n			
	Mean (SD)			
	Median			

	Min, Max			
Weight	n			
	Mean (SD)			
	Median			
	Min, Max			
BMI	n			
	Mean (SD)			
	Median			
	Min, Max			
Heart rate	n			
	Mean (SD)			
	Median			
	Min, Max			
Pre-Op Hb(gm/dl)	n			
	Mean (SD)			
	Median			
	Min, Max			
Pre-Op Albumin	n			
	Mean (SD)			
	Median			
	Min, Max			
Pre-Op Creatinine	n			
	Mean (SD)			
	Median			
	Min, Max			
SBP	n			
	Mean (SD)			
	Median			
	Min, Max			
DBP	n			
	Mean (SD)			
	Median			
	Min, Max			
RCRI Class	n			
	1			
	2			
	3			
	4			

Table 12a-b. Summary of Medical History (ITT, mITT)

Status	Statistics	Liberal Arm (N =)	Restrictive Arm (N =)	Total (N=)	p-value
Hypertension	n (%)				
Hyperlipidemia	n (%)				
Coronary artery disease	n (%)				
Congestive heart failure	n (%)				
COPD or previous active TB	n (%)				
Dementia or current change in mental status	n (%)				
MI within 6 months	n (%)				
Malnourished or cachectic	n (%)				
Cancer or current chemotherapy	n (%)				
Immunodeficiency or infection with HIV	n (%)				
Ischemic stroke or TIA	n (%)				
Prior coronary stent	n (%)				
Cardiac arrhythmias	n (%)				
MI older than 6 months	n (%)				
End stage renal disease	n (%)				
Prior coronary bypass	n (%)				
Diabetes treated with medications (oral hypoglycemic or insulin)	n (%)				
Past smoking	n (%)				
Current smoking	n (%)				

Table 13a-b. Pre-admission Ambulation and Residence (ITT, mITT)

Status	Statistics	Liberal Arm (N =)	Restrictive Arm (N =)	Total (N=)	p-value
Pre-admission Residence	n				
Retirement home	n (%)				
Nursing home	n (%)				
Rehabilitation hospital	n (%)				
Acute care hospital	n (%)				
Own residence	n (%)				
Homeless	n (%)				
Other	n (%)				
Pre-admission Ambulation	n				
Independently ambulatory	n (%)				
Ambulatory with assistance	n (%)				
Wheelchair	n (%)				
Confined to bed	n (%)				

Table 14a-b. Pre-admission Medications (ITT, mITT)

Status	Statistics	Liberal Arm (N =)	Restrictive Arm (N =)	Total (N=)
Pre-admission Medications	n			
Beta Blockers	n (%)			
Insulin	n (%)			
Other Immunosuppressant	n (%)			
Heparin	n (%)			
Diuretics	n (%)			
Oral Hypoglycemics	n (%)			
Prednisone	n (%)			
LMW heparin	n (%)			
Statin	n (%)			
ACE inhibitors	n (%)			
Plavix	n (%)			
Aspirin	n (%)			
Coumadin	n (%)			
Other oral anticoagulant	n (%)			

Table 15a-b. Post-admission Medications (ITT, mITT)

Status	Statistics	Liberal Arm (N =)	Restrictive Arm (N =)	Total (N=)
Post-admission Medications				
Coumadin Day 1 pre-op Op day (before or after Op) Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			

Status	Statistics	Liberal Arm (N =)	Restrictive Arm (N =)	Total (N=)
Heparin Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the day	n/N (%)			
LMW Heparin Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			
Oral Anticoagulant other than Coumadin Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			
Aspirin Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			
Beta-Blocker Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			
Plavix Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			

Status	Statistics	Liberal Arm (N =)	Restrictive Arm (N =)	Total (N=)
Diuretics Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			
ACE Inhibitor Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			
Insulin Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			
Oral Hypoglycemics Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			
Other Immunosuppressant Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			
Prednisone Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			

Status	Statistics	Liberal Arm (N =)	Restrictive Arm (N =)	Total (N=)
Statin Day 1 pre-op Op day Day 1 post op Day 2 post-op Discharge day Any of the days	n/N (%)			

Note: Medications on operation day does not include intraoperative medications

Table 16a-e. Primary Endpoint Analysis (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Results	Liberal (n =)	Restrictive (n =)	All Subjects (N=)
	n (%)	n (%)	n (%)
Composite event (Yes)			
Composite event (No)			
Total			
Pearson χ^2 test			
Cochran-Mantel-Haenszel test	(p =) Stratified on Clinical Centers		

Table 17a-e. Primary Endpoint Analysis, Adjusting for Baseline Age, RCRI, and Nadir Hemoglobin (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Factors	Coefficients	SE	p-Values (Wald test)	OR (95% C.I.)
Liberal vs Restrictive				
Age				

Factors	Coefficients	SE	p-Values (Wald test)	OR (95% C.I.)
RCRI 1 2 3 4				
Nadir Hb				

Table 18a-e. Summary of Secondary Outcomes (Except for Length of Stay) (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Outcomes	Liberal (N =)	Restrictive (N =)	All Subjects (N=)	$\chi 2$	p-Value
	n (%)	n (%)	n (%)		
90 Day Infectious Complications					
Present					
Absent					
Total					
90 Day Cardiac Complications					
Present					
Absent					
Total					
1 Year All-cause Mortality					
Died					
Alive					
Total					
30 Day all-cause postoperative mortality, MI, coronary revascularization, stroke, or acute renal failure					
Present					
Absent					

Outcomes	Liberal (N =)	Restrictive (N =)	All Subjects (N=)	$\chi 2$	p-Value
	n (%)	n (%)	n (%)		
Total					

Table 19a-e. Secondary Outcomes (Except for Length of Stay), Logistic Regression (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Factors	Coefficients	SE	p-Values	OR	OR 99% C.I.	
					Lower	Upper
90 Day Infectious Complications						
Liberal vs Restrictive						
Age						
RCRI 1 2 3 4						
Nadir Hb						
90 Day Cardiac Complications						
Liberal vs Restrictive						
Age						
RCRI 1 2 3 4						
Nadir Hb						
30 Day Composite Rate of All-cause Postoperative Mortality, MI, Coronary Revascularization, Stroke, or Acute Renal Failure						
Liberal vs Restrictive						
Age						

Factors	Coefficients	SE	p-Values	OR	OR 99% C.I.	
					Lower	Upper
RCRI 1 2 3 4						
Nadir Hb						
1 Year All-cause Mortality						
Liberal vs Restrictive						
Age						
RCRI 1 2 3 4						
Nadir Hb						

Table 20a-e. Summary of Length of Hospital Stay (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Intervention	Length of Hospital Stay		p-Values
	Median	Lower Quartile, Upper Quartile	
Liberal Arm			
Restrictive Arm			
Overall			

Table 21a-e. **Quantile Regression for** Length of Hospital Stay (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Factors	Coefficients, SEs and p Values		
	25^{th}	Median (50^{th})	75^{th}

Intercept			
Liberal vs Restrictive			
Age			
RCRI 1 2 3 4			
Nadir Hb			

Table 22a-e. Summary of Transfusion Related Individual Components of the Composite Endpoint (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Outcomes		Liberal (N =)	Restrictive (N =)	All Subjects (N=)	$\chi 2$	p-Value
		n (%)	n (%)	n (%)		
90-day all-cause mortality	Present					
	Absent					
	Total					
90-day MI	Present					
	Absent					
	Total					
90-day coronary revascularization	Present					
	Absent					
	Total					
90-day stroke	Present					
	Absent					
	Total					
90-day acute renal failure	Present					
	Absent					
	Total					

Table 23a-e. Transfusion Related Individual Components of the Composite Endpoint, Logistic Regression (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Outcomes		Coefficients	SE	p-Value	OR	OR 99% C.I.	
						Lower	Upper
90-day all-cause mortality	Liberal vs Restrictive						
	Age						
	RCRI 1 2 3 4						
	Nadir Hb						
	Transfusion and Age						
90-day MI	Liberal vs Restrictive						
	Age						
	RCRI 1 2 3 4						
	Nadir Hb						
90-day coronary revascularization	Liberal vs Restrictive						
	Age						
	RCRI 1 2 3 4						
	Nadir Hb						
90-day stroke	Liberal vs Restrictive						
	Age						
	RCRI 1 2 3 4						
	Nadir Hb						

Outcomes		Coefficients	SE	p-Value	OR	OR 99% C.I.	
						Lower	Upper
90-day acute renal failure	Liberal vs Restrictive						
	Age						
	RCRI 1 2 3 4						
	Nadir Hb						

Tables 24a-e. Effect of Age of Blood Transfused on Primary Outcome (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Factors	Coefficients	p-Values (Wald test)	OR (95% C.I.)
Using oldest unit transfused			
Age of Blood Transfused			
Liberal vs Restrictive			
Baseline Age of Participant			
RCRI 1 2 3 4			
Nadir Hb			
Using mean age of all the units transfused			
Age of Blood Transfused			
Liberal vs Restrictive			
Baseline Age of Participant			
RCRI 1 2			

3 4			
Nadir Hb			

Tables 25a-e. Effect of Age of Blood Transfused on 90-day Wound Infection (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Factors	Coefficients	p-Values (Wald test)	OR (99% C.I.)
Using oldest unit transfused			
Age of Blood Transfused			
Liberal vs Restrictive			
Baseline Age of Participant			
RCRI 1 2 3 4			
Nadir Hb			
Using mean age of all the units transfused			
Age of Blood Transfused			
Liberal vs Restrictive			
Baseline Age of Participant			
RCRI 1 2 3 4			
Nadir Hb			

Tables 26a-e. Effect of Age of Blood Transfused on 90-day Pneumonia (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Factors	Coefficients	p-Values (Wald test)	OR (99% C.I.)
Using oldest unit transfused			
Age of Blood Transfused			
Liberal vs Restrictive			
Baseline Age of Participant			
RCRI 1 2 3 4			
Nadir Hb			
Using mean age of all the units transfused			
Age of Blood Transfused			
Liberal vs Restrictive			
Baseline Age of Participant			
RCRI 1 2 3 4			
Nadir Hb			

Table 27a-e. Cox Regression Model for Primary Endpoint (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Factors	Coefficients	S.E.	p-Values (Wald test)	HR (95% C.I.)
Liberal vs Restrictive				
Age				
RCRI 1 2 3 4				
Nadir Hb				

Table 28a-e. Cox Regression Model for Secondary Endpoints (ITT, mITT, No-Recent-Transfusion, Completers, Per-Protocol)

Factors	Coefficients	S.E.	p-Values (Wald test)	HR (99% C.I.)
90 Day Infectious Complications				
Liberal vs Restrictive				
Age				
RCRI 1 2 3 4				
Nadir Hb				
90 Day Cardiac Complications				
Liberal vs Restrictive				
Age				

Factors	Coefficients	S.E.	p-Values (Wald test)	HR (99% C.I.)
RCRI 1 2 3 4				
Nadir Hb				
30 Day Composite Rate of All-cause Postoperative Mortality, MI, Coronary Revascularization, Stroke, or Acute Renal Failure				
Liberal vs Restrictive				
Age				
RCRI 1 2 3 4				
Nadir Hb				
1 Year All-cause Mortality				
Liberal vs Restrictive				
Age				
RCRI 1 2 3 4				
Nadir Hb				

Table 29. Cumulative SAE Incidence by Treatment Group using MedDRA Coding in Randomized Participants, by Body System and Preferred Term (Safety)

	Liberal Arm (n=)			**Restrictive Arm (n=)**			**All Subjects (N=)**		
	Participants			**Participants**			**Participants**		
Body System and Preferred Term	**N**	**(%)**	**Events**	**N**	**(%)**	**Events**	**N**	**(%)**	**Events**
All Serious Adverse Events									
Infections and infestations									
Wound infection									
Sepsis									
… and so on									

Table 30. List of SAEs where Death of Randomized Participant Is Indicated (Safety)

Center	**Ppt**	**Intervention Group**	**1. Start Date (date the SAE began)**	**Date of Death**	**Original SAE Attribution to Study**	**Detailed description of event**
…						

Table 31. Summary of Laboratory Assessment (Safety)

Time	**Assessments**	**Statistics**	**Liberal Arm**	**Restricted Arm**	**All Subjects**

			(n = ?)	(n = ?)	(N = ?)
Randomization Day	**Lowest Hemoglobin**	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest Troponin I/T	n			
		% Elevated			
	Highest Creatinine	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest CK-MB	n			
		Median			
		Interquartile Range			
		Min, Max			
Post-randomization (Day 1)	**Lowest Hemoglobin**	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest Troponin I/T	n			
		% Elevated			
	Highest Creatinine	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest CK-MB	n			
		Median			
		Interquartile Range			
		Min, Max			

Post-randomization (Day 2)	**Lowest Hemoglobin**	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest Troponin I/T	n			
		% Elevated			
	Highest Creatinine	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest CK-MB	n			
		Median			
		Interquartile Range			
		Min, Max			
Post-randomization (Day 3)	**Lowest Hemoglobin**	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest Troponin I/T	n			
		% Elevated			
	Highest Creatinine	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest CK-MB	n			
		Mean (SD)			
		Median			
		Min, Max			
Post-randomization (Day 4)	**Lowest Hemoglobin**	n			

		Median			
		Interquartile Range			
		Min, Max			
	Highest Troponin I/T	n			
		% Elevated			
	Creatinine	n			
		Mean (SD)			
		Median			
		Interquartile Range			
	CK-MB	n			
		Mean (SD)			
		Median			
		Min, Max			
Post-randomization (Day 7)	**Lowest Hemoglobin**	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest Troponin I/T	n			
		% Elevated			
	Highest Creatinine	n			
		Median			
		Interquartile Range			
		Min, Max			
	CK-MB	n			
		Median			
		Interquartile Range			
		Min, Max			
Discharge Day	**Lowest Hemoglobin**	n			
		Median			
		Interquartile Range			

		Min, Max			
	Highest Troponin I/T	n			
		% Elevated			
	Highest Creatinine	n			
		Median			
		Interquartile Range			
		Min, Max			
	Highest CK-MB	n			
		Median			
		Interquartile Range			
		Min, Max			